REMARKS

Reexamination and reconsideration of this application is respectfully requested.

Status of the Claims

In a restriction requirement dated August 25, 2003, the Examiner required restriction under 35 U.S.C. § 121 between the following groups:

Group I: Claims 50-56 and 94, drawn to a signal amplification system;

Group II: Claims 57-59, drawn to DNA library;

Group III: Claim 60-73 and 92, drawn to a method of selecting a molecule of interest and the molecule of interest;

Group IV: Claims 74-75, drawn to a kit for selecting a molecule of interest;

Group V: Claims 76-90 and 93, drawn to a method of screening for a substance, e.g., inhibitor;

Group VI: Claim 91, drawn to a kit for a substance inhibitor, for example; and

Group VII: Claim 95, drawn to a bacterial strain.

In response, applicants elected to prosecute the claims of Group I (claims 50-56 and 94). Applicants have now cancelled claims 50-95 and added new claims 96-146. Of these, claims 96-107 are drawn to a signal amplification system, and correspond to elected Group I.

Claims 108-113, 119-124, 130-135, 141, 143, and 145 are drawn to a method of selecting a molecule of interest capable of binding to a target ligand. These correspond to Group III as defined in the Restriction Requirement. Claims 114-118, 125-129, 136-140, 142, 144, and 146 are drawn to a method of screening for a substance that stimulates or inhibits the interaction between a target ligand and a molecule of interest.

These claims correspond to Group V in the Restriction Requirement. Of claims 108-146, claims 108-118, 141, and 142 depend from claim 96; claims 119-129, 143, and 144 depend from claim 100; and claims 130-140, 145, and 146 depend from claim 101.

As described above, claims 96-107 correspond to elected product claims, and claims 108-146 correspond to withdrawn claims directed to processes of using the elected claimed products. In accordance with MPEP 821.04, applicants are maintaining claims 108-146 in this application and request that they be rejoined and examined when claims 96, 100, and 101 are found allowable.

Applicants have now cancelled the claims directed to the remaining non-elected groups, and reserve the right to prosecute claims to the subject matter of those groups in one or more divisional applications.

In the Restriction Requirement, the Examiner also required that applicants elect one of various disclosed species from various claims for examination (i.e., an election of species requirement). In response, applicants elected adenylate cyclase from claim 51, and "(a) a fragment T25 corresponding to amino acids 1 to 224 of CyaA and a fragment T18 corresponding to amino acids 225 to 399 of CyaA" from claim 53, with traverse. In the Office Action, the Examiner noted applicants' traversal, but nonetheless made this election of species requirement final. Applicants respectfully request reconsideration and withdrawal of this election of species requirement for the reasons described below.

New claim 96 is directed to a signal amplification system comprising a bacterial multi-hybrid system of at least two chimeric polypeptides, a first chimeric polypeptide comprising a first fragment of an adenylate cyclase, and a second chimeric polypeptide

comprising a second fragment of the adenylate cyclase. This claim thus corresponds to applicants' election of adenylate cyclase for examination.

In claim 97, the adenylate cyclase is *Bordetella* adenylate cyclase, a species of the elected adenylate cyclase. In claim 98, it is *Bordetella pertussis* adenylate cyclase (CyaA), a species of the *Bordetella* adenylate cyclase of claim 97. In claim 99, the first and second fragments of the *Bordetella pertussis* adenylate cyclase (CyaA) are from the catalytic domain located within the first 400 amino acids of the *Bordetella pertussis* adenylate cyclase (CyaA). The first 400 amino acids of the *Bordetella pertussis* adenylate cyclase (CyaA) is a species of the *Bordetella pertussis* adenylate cyclase (CyaA) of claim 98. In claim 100, the fragments of the catalytic domain located within the first 400 amino acids of the *Bordetella pertussis* adenylate cyclase (CyaA) in the signal amplification system are chosen such that activity of the catalytic domain located within the first 400 amino acids of the *Bordetella pertussis* adenylate cyclase (CyaA) is restored by *in vivo* interaction between the molecule of interest and the target ligand, and a cAMP-mediated signal amplification is generated. This is a species of the first 400 amino acids of the *Bordetella pertussis* adenylate cyclase (CyaA) as claimed in claim 99.

Applicants have shown that claim 96 is directed to the elected adenylate cyclase species and that each of claims 97-100 reads on the elected species. Accordingly, entry and examination of these claims is appropriate at this time and respectfully requested.

Claim 101 recites a Markush group of four specific combinations of first and second fragments of the catalytic domain located within the first 400 amino acids of the

Bordetella pertussis adenylate cyclase (CyaA). As described above, in their response to the Examiner's requirement that applicants elect one of these combinations for examination, applicants elected a fragment T25 corresponding to amino acids 1 to 224 of CyaA and a fragment T18 corresponding to amino acids 225 to 399 of CyaA, from claim 53, with traverse. Applicants respectfully maintain that examination of each of the four combinations in the Markush group is appropriate.

As described in MPEP 803.02, "[I]f the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits." (emphasis added.) Applicants submit that both of these factors strongly support applicants' position that they are entitled to have the full Markush group examined in a single claim in the instant application. First, the Markush group contains only four members, which must be within the scope of "sufficiently few in number" contemplated by MPEP 803.02. Second, the members of applicants' claimed Markush group each comprise two fragments of the CyaA protein, and each of these fragments overlaps with the fragments in the other members of the group. Thus, the members are very closely related, another factor weighing in applicants' favor under the standard set forth in MPEP 803.02. For these reasons, applicants respectfully submit that the requirement that applicants elect a single member of the Markush group for examination should be withdrawn.

MPEP 803.02 further provides that if an election requirement is applied to a Markush type claim, and the elected species is found to be free of the prior art, then examination should be extended to the remainder of the claim. As the Office has cited

no prior art against applicants' claims, applicants respectfully submit that this procedure should be applied here. Applicants further request that, when the full Markush claim (now claim 101) is found to be allowable, claims 102-105, which depend from claim 101 and are each directed to a single species of the Markush group, should also be allowed. *See* MPEP 809.02(c).

Objections to the Specification

Applicants have amended the specification to remove the informalities and to add a legend to Table 2, as requested by the Examiner. Applicants submit that these amendments merely serve to make the specification even more clear, are supported by the specification as filed, and do not add new matter.

Objections to the Claims

The Office objected to a number of phrases in claim 50. Applicants note that this objection is moot in view of the cancellation of claim 50 and submit that the new claims do not contain the phrases objected to by the Office. Accordingly, withdrawal of this objection is appropriate and respectfully requested.

Claim Rejections Under 35 U.S.C. § 101 (Double Patenting)

The Office asserted that claims 50-56 and 94 claim the same subject matter as claims 1-5, 7-9, and 47 of copending Application No. 10/240,102, and provisionally rejected claims 50-56 and 94 for statutory double patenting. This rejection has been rendered moot by the cancellation of claims 50-56 and 94 herein. In the event that the

Office applies the rejection to any of the new claims, applicants courteously request that the Office hold the rejection in abeyance until conflicting claims in one of the applications are found to be allowable.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

The Office noted that "the calmodulin" in claim 55 lacks an antecedent basis. This rejection is moot in view of the cancellation of claim 55. The term "calmodulin" has proper antecedent basis as used in the new claims.

The Office also asked for clarification as to the polynucleotide and polypeptide sequences referred to by "CyaA" in the specification and claims. In response, Applicants note that the application states that CyaA is the adenylate cyclase described in WO 99/28746. (Application at page 25, lines 13-16.) Applicants have attached WO 99/28746 hereto as Exhibit A. At page 12 of Exhibit A, Glaser et al., *Molecular Microbiology*, Vol. 2(1), pp. 19-30 (1988), is cited as disclosing the sequence of CyaA. Applicants have attached a copy of Glaser et al., *Molecular Microbiology*, Vol. 2(1), pp. 19-30 (1988) hereto as Exhibit B. Exhibit B discloses the cloning of CyaA and provides the sequence of CyaA.

Solely by way of clarification, applicants note that, because CyaA was well known to the skilled artisan as of their effective filing date there was no need to present CyaA nucleotide and/or protein sequences in their application. *See, e.g., Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534, 3 U.S.P.Q.2d 1737, 1743 (Fed. Cir. 1987), *citing Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384,

231 U.S.P.Q. 81, 94 (Fed.Cir.1986) (noting that applicants need not teach, and preferably omit descriptions of well known information from a patent application).

Claim Rejections Under 35 U.S.C. § 112, First Paragraph (Enablement)

The Office rejected claims 51-53, 55, and 56 under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement. (Office Action at pages 4-9.) This rejection has been rendered moot by the cancellation of the rejected claims. As applicants will show, the new claims are fully enabled and this rejection should not be applied to them.

First, the Office rejected the cancelled claims on the basis that they recite novel *E. coli* strain **BTH101**, having C.N.C.M. Deposit Accession No. I-2309, and novel *E. coli* strain **DHM1**, having C.N.C.M. Deposit Accession No. I-2310. The Office stated that these novel cells were essential to the claimed invention, and asserted that they "must be obtainable by a repeatable method or otherwise be readily available to the public." (Office Action at page 5.) The Office further indicated that this rejection could be overcome by a deposit of the cells, and acknowledged that a deposit had been made, as indicated at pages 15-16 of the application. (Office Action at page 5.) However, the Office requested some assurance regarding the public availability of the deposited cells. (Office Action at page 5.)

In response, Applicants file herewith a Deposit Declaration executed by Danielle Berneman of Institut Pasteur, an Assignee of the instant application (the "Berneman Declaration"). The Berneman Declaration states that "*E. coli* strains BTH101 and DHM1, disclosed in this application, were deposited on September 10, 2003, under the

provision of the Budapest Treaty at the National Collection of Cultures of Microorganisms (C.N.C.M.) in Paris, France, and assigned Accession Nos. I-2309 and I-2310, respectively, to assure availability to the public." The Berneman Declaration further states that "the C.N.C.M. has acquired the status of International Depository Authority within the meaning of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure." The Berneman Declaration further states that the "*E. coli* strains have been deposited under conditions which ensure that access to the strains will be available during the pendency of this patent application to one determined by the Commissioner of Patents and Trademarks to be entitled thereto under 37 C.F.R. § 1.14 and 35 U.S.C. § 1.22." Finally, the Berneman Declaration also states that "Institut Pasteur will replace the deposited strains BTH101 and DHM1 should they become non-viable during the period that extends thirty (30) years from the date of the deposit, or the period of the enforceable life of the patent, or the period of five years after the last public request for the deposit, whichever period is longest." Applicants submit that the Berneman Declaration satisfies the requirements of 37 C.F.R. §§ 1.801-809 and demonstrates that Applicants have enabled the use of strains BTH101 and DHM1. Accordingly, Applicants submit that this rejection should not be applied to the new claims.

The Office also rejected cancelled claims 50-52, 54-56, and 94 on the basis that the specification allegedly "does not provide enablement for any signal amplification system comprising a first peptide comprising any fragment of any enzyme, or any fragment of any adenylate cyclase, linked to a molecule of interest and a second peptide comprising any fragment of any enzyme, or any fragment of any adenylate

cyclase, or any modulating substance thereof, linked to a target ligand." (Office Action at page 6.) The Office further contends that the specification is not enabling for an amplification system comprising a mutated fragment of the catalytic domain of *Bordetella* adenylate cyclase (CyaA). (Office Action at page 6.) While this rejection has been rendered moot by cancellation of the rejected claims, Applicants respectfully submit the following arguments in support of the enablement of the new claims.

In assessing enablement, the relevant inquiry is whether one of skill in the art could practice the invention as claimed based on the disclosure in the specification, coupled with information known in the art, without undue experimentation. *See* M.P.E.P. § 2164.01. Factors relevant to determining whether an undue amount of experimentation would be necessary to practice an invention as claimed include (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of ordinary skill in the art; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. M.P.E.P § 2164.01(a), *citing In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). An analysis of these factors as applied to the new claims demonstrates that the new claims are enabled.

Regarding *Wands* factor 2, the claims are directed, generally, to a signal amplification system comprising a bacterial multi-hybrid system of at least two chimeric polypeptides. The first chimeric polypeptide comprises a first fragment of the catalytic domain of an adenylate cyclase and a molecule of interest fused to the first fragment. The second chimeric polypeptide comprises a second fragment of the catalytic domain

of an adenylate cyclase and a target ligand fused to the second fragment. When activity of the adenylate cyclase is restored by *in vivo* interaction between the molecule of interest and the target ligand, a cAMP-mediated signal amplification is generated. The signal amplification is performed in *E. coli* strain BTH101 having C.N.C.M. Deposit Accession No. I-2309 or *E. coli* strain DHM1 having C.N.C.M. Deposit Accession No. I-2310. The signal amplification system is the basis for the claimed methods of selecting a molecule of interest capable of binding to a target ligand, and the claimed methods of screening for a substance that stimulates or inhibits the interaction between a target ligand and a molecule of interest.

Regarding *Wands* factor 1, Applicants note that the new claims do not recite "any enzyme," but rather recite first and second fragments of the catalytic domain of an adenylate cyclase (claim 96); first and second fragments of the catalytic domain of a *Bordetella* adenylate cyclase (claim 97); first and second fragments of the catalytic domain located within the first 400 amino acids of the *Bordetella pertussis* adenylate cyclase (CyaA) (claim 98); first and second fragments of the catalytic domain located within the first 400 amino acids of the *Bordetella pertussis* adenylate cyclase (CyaA), which are complementary fragments (claim 99); first and second fragments of the catalytic domain located within the first 400 amino acids of the *Bordetella pertussis* adenylate cyclase (CyaA), wherein the first and the second fragments of the catalytic domain of the *Bordetella pertussis* adenylate cyclase (CyaA) *in vitro* functionally interact with a natural activator of the *Bordetella pertussis* adenylate cyclase (CyaA) by restoring the activity of the catalytic domain of the *Bordetella pertussis* adenylate cyclase (CyaA) (claim 100); or specific combinations of fragments corresponding to specific amino acid

sequences of the catalytic domain of CyaA (claims 101-105). Applicants further note that the new claims do not recite "a mutated fragment," and also do not recite "a modulating substance capable of activating said enzyme."

Adenylate cyclase enzymes were well known in the art as of the March 29, 2000, filing date of priority application No. 60/192,886. For example, an article by James H. Hurley, titled "The Adenylyl and Guanylyl Cyclase Superfamily," was published in *Current Opinion in Structural Biology*, Vol. 8, pp. 770-77 (1998) (attached hereto as Exhibit C), and describes the structure of adenylate cyclase enzymes from various species. One of skill in the art was also able to use fragments of the catalytic domain of adenylate cyclase enzymes to make active enzymes. For example, an article by Tang et al., titled "Construction of a Soluble Adenylyl Cyclase Activated by $G_s\alpha$ and Forskolin," was published in *Science*, Vol. 268, pp. 1769-1772 (1995) (attached hereto as Exhibit D), and describes that fusion proteins comprising two fragments of the catalytic domain of mammalian adenylate cyclase are active. Similarly, an article by Tesmer et al., titled "Crystal Structure of the Catalytic Domains of Adenylyl Cyclase in a Complex with $G_s\alpha$ •GTPγS," was published in *Science*, Vol. 278, pp. 1907-16 (1997) (attached hereto as Exhibit E), and describes that individual domains of the catalytic domain of adenylyl cyclase, which on their own have very little catalytic activity, can be combined to restore catalytic activity. (Exhibit E at page 1907, middle col.) These references make clear that the state of the art as of March 29, 2000, was that many adenylate cyclase enzymes from diverse species were known, that the catalytic domains of these adenylate cyclase enzymes had been defined, and that one of skill in the art was able to combine fragments of the catalytic domains of the various enzymes

to restore the catalytic domain's activity. (*Wands* factors 3 and 4.) These references also demonstrate that it was predictable that recombining fragments of catalytic domains from an adenylate cyclase enzyme would form an active adenylate cyclase catalytic domain. (*Wands* factor 5.)

The Office's position that the canceled claims were not enabled appears to be based primarily on its conclusion that one of skill in the art would not know which fragments of an adenylate cyclase catalytic domain can be used to practice the claimed invention. Applicants submit that the working example of a signal amplification system presented in the application (*Wands* factor 7), which uses the T25 and T18 fragments of the catalytic domain of the *Bordetella pertussis* adenylate cyclase catalytic domain, demonstrates convincingly to one of skill in the art that the signal amplification system works when fragments of a catalytic domain of an adenylate cyclase enzyme are used to practice the claims. (*Wands* factor 6.) This is all the more so in regard to *Bordetella* adenylate cyclase enzymes. In fact, an article by Betsou et al., titled "Cloning and Sequence of the *Bordetella bronchiseptica* Adenylate Cyclase-Hemolysin-Encoding Gene: Comparison with the *Bordetella pertussis* Gene," was published in *Gene*, Vol. 162, pp. 165-66 (1995) (attached hereto as Exhibit F), and teaches that the catalytic domains of the adenylate cyclase enzymes from *Bordetella bronchiseptica* and *Bordetella pertussis* contain only four amino acid differences. (Exhibit F at page 166, left col.) In view of this high degree of sequence conservation among *Bordetella* adenylate cyclase enzymes, and the many adenylate cyclase enzymes known in the art, one of skill in the art would conclude on the basis of Applicants' disclosure and in view

of the art, that Applicants' claims can be practiced throughout their full scope without undue experimentation.

Applicants also note that the Office has not provided any reason why one of skill in the art, armed with Applicants' disclosure of a working example, and aware of the prior art teachings regarding adenylate cyclase enzymes, would not consider Applicants' teachings and statements made in the application as applying to the full breadth of the invention as claimed. Absent such a reason, Applicants submit that the enablement rejection can not be properly applied to the new claims.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph (Written Description)

The Office rejected claims 50-52, 54-56, and 94 under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. (Office Action at page 10.) This rejection has been rendered moot by the cancellation of the rejected claims. As applicants will show, the new claims are fully supported by an adequate written description and this rejection should not be applied to them.

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention." (*Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998) (internal quotes omitted). The written description requirement may be met

for a claimed genus "by disclosure of relevant, identifying characteristics, i.e., such as structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus." MPEP 2163(II)(A)(3)(a)(ii), *citing Eli Lilly*. Applicants' specification meets this standard as to the new claims.

Specifically, the new claims all recite "an adenylate cyclase catalytic domain," differing only as to the scope of the adenylate cyclase that is claimed. The Office characterizes Applicants' disclosure as "teach[ing] the structure of only a single representative species of [signal amplification] system[]: the CyaA system using the T25 and T18 fragments." (Office Action at page 10.) However, the application states that "[a]ccording to one embodiment of the invention, the enzyme can be selected from the group consisting of adenylate cyclase and guanylate cyclase from any origin." (Application at page 25, lines 11-12.) This statement, coupled with the numerous adenylate cyclases having known catalytic domains (i.e., known structures) available in the art as of Applicants' effective filing date is effectively a reference to each known species of adenylate cyclase, and a statement that each one is within the scope of an embodiment of the invention. Applicants submit that in this way the application demonstrates possession of the full breadth of the invention defined by the new claims when this application was filed and that, therefore, the new claims are supported by an adequate written description. Thus, no rejection for lack of adequate written description should be applied to the new claims.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims 96-146.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: July 26, 2004

By: _____
Kenneth J. Meyers
Reg. No. 25,146

Attachments: New Abstract
Exhibits A-F

PATENT
Customer No. 22,852
Attorney Docket No. 3495.0202

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Group Art Unit: 1652
Gouzel KARIMOVA et al.	Examiner: Sheridan Swope
Application No.: 09/818,939	
Filed: March 28, 2001	
For: BACTERIAL TWO-HYBRID SYSTEM FOR PROTEIN-PROTEIN INTERACTION SCREENING, NEW STRAINS FOR USE THEREIN, AND THEIR APPLICATIONS	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DEPOSIT DECLARATION

I, Danielle Berneman, do hereby declare and say that:

1. I am the Head of the Patent Section of the Institut Pasteur in Paris, France, to whom this patent application has been assigned.

2. On information and belief, *E. coli* strains BTH101 and DHM1, disclosed in this application, were deposited on September 10, 2003, under the provision of the Budapest Treaty at the National Collection of Cultures of Microorganisms (C.N.C.M.) in Paris, France, and assigned Accession Nos. I-2309 and I-2310, respectively, to assure availability to the public.

3. On information and belief, the C.N.C.M. has acquired the status of International Depository Authority within the meaning of the Budapest Treaty on the

International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure.

4. Said *E. coli* strains have been deposited under conditions which ensure that access to the strains will be available during the pendency of this patent application to one determined by the Commissioner of Patents and Trademarks to be entitled thereto under 37 C.F.R. § 1.14 and 35 U.S.C. § 1.22.

5. On information and belief, Institut Pasteur will replace the deposited strains BTH101 and DHM1 should they become non-viable during the period that extends thirty (30) years from the date of the deposit, or the period of the enforceable life of the patent, or the period of five years after the last public request for the deposit, whichever period is longest.

6. I further declare that all statements made herein of my own knowledge are true; that all statements made on information and belief are believed to be true; that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 21th day of July, 2004

Danielle Berneman
Head of Patents and Inventions
Institut Pasteur

Danielle BERNEMAN
Chef du Service des Brevets
& Inventions